UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,227	03/06/2006	John S. Haurum	63573(50533)	6313

21874 7590 08/19/2008

EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
08/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,227	HAURUM ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40 and 48-52* is/are pending in the application.

4a) Of the above claim(s) *3,14,18,21-40 and 48-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-13,15-17,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election with traverse of Group I, claims 1-20 is acknowledged. The traversal is on the ground(s) that the subject matter of these groups represents different embodiments of a single inventive concept for which a single patent should issue. The pending claims represent an intricate web of knowledge, continuity of effort, and consequences of a single invention, which merit examination of all of these claims in a single application. More particularly, special technical features under Rule 13.2 PCT link all of the claims. This single, searchable, unifying aspect comprises the discovery that a collection of cells may be used to express polyclonal proteins, each of which binds a particular antigen. Moreover, each distinct member of these polyclonal proteins is expressed using an expression construct that has been integrated into the genome of each cell at a specific integration site. In addition, Applicants submit that a sufficient search and examination with respect to the subject matter of all claims can be made without serious burden. As the M.P.E.P. states: If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though

it includes claims to independent or distinct inventions. M.P.E.P. § 803 (8th ed., Rev. No. 2, May 2004). That is, even if the above-enumerated groups of claims are drawn to distinct inventions, the Examiner must still examine the entire application on the merits because doing so will not result in a serious burden. This is especially true given the robust and extensive computerized search engines and databases at the Examiner's disposal. Moreover, Applicants note that the entire application was searched by the international Examiner, and that the International Search Report was provided to the U.S. Patent and Trademark Office at the time of. This is not found persuasive because as stated by applicants above the claims are drawn to independent and distinct inventions. The examination of this distinct and independent subject matter would impose undue examination to the examiner. Although a robust and extensive computerized search engines and databases are at the examiner's disposal however each of the commercial databases as well as patents (US and foreign) are not co-extensive. Although a search was done by an international examiner, however this does not relief the US examiner of searching the claimed invention and applying the statutory requirement for a patent grant. Thus, to

examine all the 53 claims would impose an undue burden to the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Applicants' further election of the following species: ELISA-screening procedure, CHO cell line- mammalian cell lines and the T-cell receptor-polyclonal antibody is likewise acknowledged.

Claims 21-40 and 48-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement on 6/02/08.

Status of Claims

Claims 1-40 and 48-52 are pending.

Claims 3, 14, 18, 21-40 and 48-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions and species.

Claims 1-2, 4-13, 15-17 and 19-20 are under examination.

Specification

The abstract of the disclosure is objected to because it uses the PCT abstract. Correction is required. See MPEP § 608.01(b).

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors (typographical, grammatical and idiomatic). Applicants' cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17 and 19-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 17 is unclear as to the language "library comprises a naturally occurring diversity located within the variant nucleic acid sequences" is confusing as to the scope of what is being claimed.

2. In claim 19 “fine” should be ---line---. Also, the term “type" in claim 10 is a relative term which renders the claim indefinite.

3. The metes and bounds of cell lines "derived thereof" is unclear as to what would be considered a derivative or the source of said cell line from which the cell is derived. Claim 20.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-13, 15-17 and 19-20 are rejected under 35 U.S.C. 102(a or e) as being anticipated by Huse et al (WO 02/44361)(corresponds to US 20030096401.)

Huse et al discloses throughout the patent at e.g., page 16, line 24 up to page 20, line 10::

> One approach for targeting variant or heterologous nucleic acids to a single site in the genome uses Cre recombinase to target insertion of exogenous DNA into the eukaryotic genome at a site containing a site specific recombination sequence…… of the core region (Figure 5A, arrows). Cre recombinase also catalyzes site-specific recombination in eukaryotes, including both yeast and mammalian cells…… Homologous recombination can also be used to locate a nucleic acid sequence at a particular site in the genome. For example, a vector can be designed so that an individual nucleic acid of a population of nucleic acids is flanked by nucleic acid sequences having sufficient homology to allow homologous recombination with a homologous nucleic acid sequence located at a particular site in the genome of a cell. Such a homologous sequence can naturally occur at a particular genomic location or the homologous sequence can be introduced recombinantly using well known methods of transfection and using vectors that allow integration into the host genome. If the homologous sequence is introduced into the genome recombinantly, a cell line can be clonally isolated so that cells of a given clone will have the homologous sequence located at the same genomic site. Methods of introducing a nucleic acid into the genome at a particular site using homologous recombination use the endogenous recombination machinery rather than an exogenous recombinase such as Cre or Flp.

Huse et al further discloses at e.g., page 7, lines 1-19:

> …Compositions comprising a population of non-yeast eukaryotic cells containing a diverse population of variant nucleic acids or heteroiogous nucleic acids and methods of using the populations. The compositions comprise a population of non yeast eukaryotic cells containing a diverse population of variant nucleic acids or heterologous nucleic acids, each species of nucleic acid being expressed in a different cell and located within each cell at an identical site in the genome. The compositions and methods are advantageous in that the nucleic acid in a population of nucleic acids can be expressed in a separate cell to

minimize complications associated with transfection of multiple species in the .... same cell. The nucleic acids can also be targeted to the same site in the cell genome, for example, using site- specific recombination, to generate isogenic cells expressing the nucleic acids....

Huse et al discloses at e.g., page 10, lines 15-30:

Receptors can include antibodies and can include other polypeptides or ligands of the immune system. Such other polypeptides of the immune system include, for example, T cell receptors (TCR), major histocompatibility complex (MHC), CD4 receptor and CD8 receptor.

Huse discloses at e.g., page 13, line 10 up to page 14,

line 15:

……"Population"…. refer to a group of two or more different molecules. A population can be as large as the number of individual molecules currently available to the user or able to be made by one skilled in the art. Typically, populations can be as small as 2 molecules and as large as i0~3 molecules. In some embodiments, populations are between about 5 and 10 different species as well as up to hundreds or thousands of different species. In the specific example presented in Example V, the population described therein is 7 different species. Example IX exemplifies populations of about 200 to about 1300…

Accordingly, the specific method of Huse using specific components in the method anticipates the broad claim method.

Claim 1 is rejected under 35 U.S.C. 102(a or e) as being anticipated by Greener et al(USP 6368821).

Greener discloses throughout the patent at e.g., col.8,

line 34 up to col.9, line 60:

A method to confirm that a complex lambda library may be screened for a unique clone of interest directly in a mammalian cell. As a first example, a "mock" library that contains a readily assayable gene will be screened. This will be performed by taking a ZAP Express premade library of phage and mixing it with 1, 10, 100, 1000 or 10,000 lambda phage that express the Green Fluorescent Protein. The library will also be exposed to a second lambda (ZAP Express containing neoR). Both stably and transiently transfected cell lines will be tested to evaluate at what relative concentration the GFP-lambda is found, and whether these transfectants will also have been infected by the non-selected second lambda, and thus become G418 resistant. If the lambda-GFP phage can be recovered when present in a minority of the total phage, the system should be amenable for direct library screening. The possibility that more than a single lambda will enter a cell will be exploited for the development of a mammalian 2-hybrid system.

Greener further discloses at e.g., col. 8, line 57 up to

col. 9, line 60:

(a) Construction of lambda library vectors that permit direct functional cloning of cDNA libraries. These vectors will have the GFP reporter gene (that is expressed from an internal ribosome entry site) or the G418.sup.R (neo.sup.R) gene for selection/screening. These vectors will contain promoters to direct high levels of expression of the cloned gene.
(b) To determine possible variants with improved properties, PCR will be used to determine whether all or parts of lambda genome become incorporated in given cell lines. Also, tests will be performed to determine if there are preferred sites of integration.
(c) Inclusion of loxP sites and the cre recombinase gene of phage P1 for the in vivo excision of the cloned gene of interest upon entry into the cell. In addition, the Epstein-Barr virus origin of replication and EBNA-1 gene will be inserted within the loxP sites to permit stable episomal replication in the infected cell line.

Accordingly, the specific method of Greener using specific process steps and components therein anticipates the broad claim method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 5-12, 17 and 19-20 are rejected under 35 U.S.C. 102(b)) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over anyone of Biard-Piechaczyk et al (Human antibodies, 1999) or Tsurushita et al (Gene, 1996) or Zahra et al (Gne, 1999).

Biard-Piechaczyk et al discloses throughout the article, at e.g., page 67, abstract a method of producing cells comprising human scFv display library with Cre recombinase induction. See specifically a detail description of the method at pages 67-71.

Tsurushita et al discloses throughout the article specifically at page 60 under Experimental Discussion a method of producing cells comprising ScFv and recombinase.

Zahra et al discloses throughout the article a method of producing a library of cells comprising recombination at the lox P cites. See pages 49-52.

Accordingly, each of the processes steps of Biard-Piechaczyk, Tsurushita and Zahra fully meets or render obvious the broad claimed method using broad components therein.

[MPEP 706.02 states that a rejection under 102/103 is proper when the (broad) claimed invention is subject to several interpretations.]

Claims 1-2, 4-13, 15-17 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over anyone of Huse or Biard-Piechaczyk et al (Human antibodies, 1999) or Tsurushita et al (Gene, 1996) or Zahra et al (Gene, 1999)in view of Reff et al (WO 98141645).

Each of Huse, Biard-Piechaczyk et al, Tsurushita et al and Zahra et al is discussed above. Each of these references does not teach that the cell is CHO cell line. However,

Reff discloses throughout the patent at e.g., page 13, lines 5-10:

> ….CHO cell lines which contain immunoglobulin genes integrated at predetermined sites that provide for high expression, and have been amplified by methotrexate selection to secrete even greater amounts of functional immunoglobulins.

Accordingly, it would be obvious to one having ordinary skill in the art at the time the invention was made to use CHO as the cell line in anyone of the method of e.g., Huse et al for the advantage as taught by Reff. One would have a reasonable expectation of success in using CHO cell line. This cell line is the mammalian cell line normally use in the art for its high expression of integrated genes as taught by Reff.

No claim is allowed.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Robl (20030044398) teaches monoclonal or polyclonal antibodies.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0765. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/TERESA WESSENDORF/

Primary Examiner, Art Unit 1639